



# Mesothelioma from asbestos exposures: Epidemiologic patterns and impact in the United States

Richard A. Lemen

**To cite this article:** Richard A. Lemen (2016) Mesothelioma from asbestos exposures: Epidemiologic patterns and impact in the United States, Journal of Toxicology and Environmental Health, Part B, 19:5-6, 250-265, DOI: [10.1080/10937404.2016.1195323](https://doi.org/10.1080/10937404.2016.1195323)

**To link to this article:** <http://dx.doi.org/10.1080/10937404.2016.1195323>



Published online: 05 Oct 2016.



Submit your article to this journal [↗](#)



View related articles [↗](#)



View Crossmark data [↗](#)

## Mesothelioma from asbestos exposures: Epidemiologic patterns and impact in the United States

Richard A. Lemen

Department of Environmental Health, Emory University, Atlanta, Georgia, USA

### ABSTRACT

Mesothelioma, a rare tumor, is highly correlated with asbestos exposure. Mesothelioma, similar to all asbestos-related diseases, is dose/intensity dependent to some degree, and studies showed the risk of mesothelioma rises with cumulative exposures. Multiple processes occur in an individual before mesothelioma occurs. The impact of mesothelioma in the United States has been continuous over the last half century, claiming between 2,000 and 3,000 lives each year. Mesothelioma is a preventable tumor that is more frequently reported as associated with asbestos exposure among men than women. However, the rate of asbestos-associated mesothelioma is on the rise among women due to better investigation into their histories of asbestos exposure. It is of interest that investigators detected asbestos-associated cases of mesothelioma in women from nonoccupational sources—that is, bystander, incidental, or take-home exposures. It is postulated that asbestos-associated mesotheliomas, in both men and women, are likely underreported. However, with the implementation of the most recent ICD-10 coding system, the correlation of mesothelioma with asbestos exposure is expected to rise to approximately 80% in the United States. This study examined the demographic and etiological nature of asbestos-related mesothelioma.

Questions often arise as to what exposures to asbestos contribute to mesothelioma. In answering this question, it is important to understand both historical as well as current knowledge related to etiology and epidemiology. This study addresses such knowledge, including the role of multiple exposures to asbestos. However, as the potencies of asbestos fiber types have been discussed in detail elsewhere, this topic is not addressed in this article (Aust, Cook, and Dodson 2011; Cyphert et al. 2015; Henderson, Shilkin, and Langlois 1992; IARC 2012; IPCS 1998; Lemen 2011; Nicholson 2001; Robinson and Chahinian 2002; Stayner, Dankovic, and Lemen 1996; Wylie and Candela 2015).

### Demographics of mesothelioma

There is no dispute that asbestos produces mesothelioma, and that the great majority of mesotheliomas are induced by asbestos (Checkoway, Pearce, and Crawford-Brown 1989; CR, 1997; Collegium Ramazzini 2015b; IARC 2012; Krupoves, Camus, and De Guire 2015; Lemen 2014; Lemen and

Dodson 2012; Marinaccio et al. 2015; Markowitz 2015; Mullan and Murthy 1991; Steenland et al. 2003; Wolff et al. 2015). Mesotheliomas where no causal risk factor is identified are sometimes referred to as “idiopathic.” Some mesotheliomas are never linked to asbestos exposure, either because (1) there is no known history of exposure to asbestos; (2) subjects die before an exposure history is obtained; or (3) when seeking a history of potential asbestos exposure from a next of kin, the next of kin have no knowledge of any asbestos exposure. In addition, while many epidemiological studies assess occupational exposure, these neglect to investigate potential para-occupational or environmental exposures to asbestos. Thus, an initial conclusion that a mesothelioma subject had no asbestos exposure needs to be viewed with skepticism. In fact, in one case where investigators probed deeper for any asbestos relationship, 81% of those previously reported with no history of asbestos exposure were found to have transmission electron microscopy (TEM) lung asbestos fiber counts >200,000 fibers >2  $\mu\text{m}$  length per gram dry lung tissue, thereby suggesting unrecognized exposures (Leigh et al. 2002).

### **Mesothelioma among men and women**

Mesothelioma is more frequently reported among men than among women in the United States, but this has not been true in all countries. In-depth analysis revealed that mesothelioma is not a male-dominated disease and that given similar exposures to asbestos, women are just as susceptible (Barbieri, Migliori, and Merier 1999; Newhouse and Berry 1976, 1979; Pira et al. 2005; Szeszenia-Dabrowska et al. 2002). Mesothelioma has been more frequently reported in women from nonoccupational exposure sources, such as bystander, incidental, or take-home exposure (NIOSH 1995).

Pira et al. (2005) found the standard mortality ratio (SMR) values were higher in women asbestos textile workers for pleural, peritoneal, and lung cancer.<sup>1</sup> Newhouse and Berry (1976) reported a total excess mortality factor of 2.6 for women compared to 1.7 for men with 2 years or more of severe asbestos exposure, although the overall mesothelioma rate per 100,000 was higher for men (221) than for women (104). In a later study of London (UK) factory workers, mesothelioma occurred in 16% of the 4600 deceased men ( $n = 775$ ) and 24% of deceased women (225), even though women accounted for only 16% of the total cohort. In the whole worker cohort, women with less than 2 years of asbestos exposure had a higher mesothelioma rate (136/100,000) compared to men (104/100,000). Similarly, for workers with greater than 2 years of asbestos exposure, women had a higher rate of mesothelioma of 360/100,000, compared to men with 243/100,000. Both male and female mesothelioma death rates were clearly related to degree and length of exposure to asbestos (Newhouse and Berry 1979). Wang et al. (2013) reported significant increases in mesothelioma and ovarian cancer among women in a chrysotile factory that did not begin hiring females until 1970.

Jones et al. (1988) noted that overall death ratios in men and women for pleural (4.6:1) and peritoneal (2:1) mesotheliomas were different, but when evaluating age-specific death rates the divergence in pleural mesothelioma was absent for peritoneal mesothelioma. Reid et al. (2014) observed, after studying 6 asbestos exposed cohorts (5 from Italy and 1 from Australia), that women displayed

longer latencies for both peritoneal mesothelioma after 40 years since first exposure (81% compared to 47% in men) and pleural mesothelioma (60% compared to 40% in men).

Röesler et al. (1994) observed that for 616 German female workers exposed to asbestos, the death rates for mesothelioma were 340-fold higher than in the general population, and were fourfold higher than in men. For nonoccupational exposures to asbestos, McDonald (1980) reported that removing all men and women with known occupational or mining exposures to asbestos revealed that the rates for mesothelioma for those living in the asbestos chrysotile mining area were similar in both women and men. McDonald (1980) suggested, "It seems possible that these cases may have some other etiology." However, some years later, Camus, Siemiatycki, and Meek (1998) noted that women living in the asbestos mining areas of Quebec showed a significantly elevated SMR of 7.63 (95% CI: 3.06–15.73) for pleural cancer and a significantly increased SMR for asbestosis (23.49; 95% CI: 2.64–84.83). Accordingly, Camus, Siemiatycki, and Meek (1998) concluded that this supported a nonoccupational asbestos etiology for pleural cancers.

A review using the SEER<sup>2</sup> data comparing anatomical location of mesothelioma found the rate of peritoneal mesothelioma (14.8%) in women almost threefold greater compared to men (5.4%), but a higher rate for pleural mesothelioma occurring in men (Larson et al. 2007). Neumann et al. (2004) reported that women developed mesothelioma at a younger age than men (on average 4.5 years), but that males were approximately 1.5 years older at time of death.

Citing Pinton et al. (2009) for the theory that the estrogen receptor (ER $\beta$ ) may play a role in malignant mesothelioma cell proliferation, Linton et al. (2012) reported a "multivariate analysis revealing ER beta expression to be an independent prognostic factor in MM [malignant mesothelioma] (HR 0.2) with higher expression noted in females (21.1% versus 13.6%)." They cautioned that it is unclear whether the receptor expression offers a protective effect against developing mesothelioma, noting that the Wittenoom (Australia) cohort had a higher rate of mesothelioma in men than in women, even after adjusting for cumulative asbestos exposure and age at first residence, although females had a steeper dose-response slope.

If a differential relationship between asbestos-related mesothelioma incidence found in men as contrasted with women, this finding may well be associated with the historic dissimilarity of occupational exposures to asbestos and/or a failure to associate female mesothelioma with environmental or take-home asbestos exposures. Steenland et al. (2003) stated, “For women the overall attributable risk was 23%. If the deaths due to ‘take-home’ asbestos exposure were considered, the attributable risks may be around 90%.” Additionally, Leigh et al. (2002) stated, “Past exposure is not always recognized as such and this is more likely to be the case in females.” These statements suggest that inadequate exposure history ascertainment and failure to consider homogeneity within exposure patterns between the sexes might account for reported differences in rates of mesothelioma.

It is also important to note Peto et al. (2009), when discussing the annual number of unexplained mesotheliomas, which were similar in men and women, observed:

This unexplained rate accounts for almost two-thirds of our female cases, so the threefold increase since 1970 in the overall British female death-rate below age 65 implies at least a doubling in this “background” female rate. Most of this increase has occurred in the last 10 years, so it seems likely to be due to an increase in ambient asbestos exposure that coincided with the widespread occupational exposures of the 1960s and 1970s rather than to an increase in diagnostic awareness. (Peto et al., 2009, 45)

### ***Genetic susceptibility, age, and mesothelioma***

Suggestions of genetic susceptibility for mesothelioma have come from observations of familial clusters in Italy and studies of erionite exposed families in Turkey (Ascoli, Mecucci, and Knuutila 2001, 2007, 2014; Baris et al. 1979; Carbone et al. 2011; Cheung et al. 2015; 2016; Crovella et al. 2016; Metintas, Hillerdal, and Metintas 1999). However, a precise genetic role in familial susceptibility for mesothelioma has yet to be determined.

Carbone et al. (2007) and Yang, Testa, and Carbone (2008) both suggested genetic predisposition and or environmental exposures to carcinogenic mineral fibers occurring from an early age as possible etiological factors. While it is thought that

most familial clusters of mesothelioma are related to mutual asbestos exposures, there remains a suggestion that additional contributing factors such as genetic susceptibility may play a role (Ugoilini et al. 2008).

What is known about a genetic role in the etiology of mesothelioma relates to autosomal dominant inheritance found with high familial rates of mesothelioma in the Cappadocia region of Turkey (Roushdy-Hammody et al. 2001). Testa et al. (2012) noted germline BAP1 mutations in some mesothelioma-prone families having little history of heavy exposure to asbestos. However, Sneddon et al. (2015) reported in their 115 malignant mesothelioma cases that after using targeted resequencing, no BAP1 germline mutations of known functional significance were identified and that variations found in the sample population were consistent with the expected rate for an outbred population. This finding supports two other studies (Betti et al. 2015; Rusch et al. 2015) showing no known functionally significant BAP1 germline mutations. However, other investigators still consider mutations of the BAP1 gene as potential markers for susceptibility and, while currently biomarkers for malignant pleural mesothelioma are not satisfactory, do believe that specific noninvasive markers will emerge (Panou et al. 2015).

Mesothelioma is rarer among those less than 40 years of age. Analyzing data collected from the SEER database from 1990 through 2010, 1.7% of mesotheliomas occurred in those below 40 years of age, with a 51/49% male/female ratio, which contrasted with the significantly different 78/22% male/female ratio for those in the 40 year and older category (Thomas et al. 2015). In the less than 40 years age group, mesothelioma was more frequently reported among whites than any other racial groups, and anatomical sites for the over 40 years age group were striking, with 90% pleural versus 9% peritoneal. Histologic subtype was not available for the majority of cases, but for those where it was known epithelioid was the most common. In the younger age group, 49% of the cases occurred between ages of 35 and 40 years of age in both genders. Regardless of histologic subtype, median survival time for the under 40 years old mesothelioma patients was 34 mo, compared

to 8 mo in those older. Mesothelioma found in young patients was less likely to be due to occupational asbestos exposures as opposed to household or para-occupational exposures. The 5-year survival rate for the under 40 years age group was 38%, compared to 3% in the over 40 years age group. Variables associated with better survival included female gender, peritoneal tumor, receipt of site-directed surgery, and radiation. Reid et al. (2014) observed that the elevation in incidence of pleural mesothelioma fell after 45 years since first exposure, while peritoneal tumors continue increasing.

Dragon et al. (2015) found significantly greater changes in genome-wide expression in response to asbestos exposure in pleural mesothelioma cells compared with peritoneal mesothelioma cells, which required a higher dose of asbestos for such changes. This is consistent with some epidemiology reporting higher asbestos exposures among peritoneal mesothelioma cases (Lemen and Dodson 2012).

### **Mesothelioma reporting, incidence, and diagnosis**

Mesothelioma, still a rare tumor, is generally detected after 30–40 years of development. It is likely underreported and remains difficult to diagnosis, requiring a battery of tissue staining that only a limited number of facilities are able to perform. Prior to the introduction of the ICD-10 coding system in the late 1990s mesothelioma was coded under multiple codes, which led to misclassification (Pinherio et al., 2004). For this reason, in the United States, SEER incidence data provide the best glimpse into its occurrence rate (Steenland et al. 2003). The average annual age-adjusted incidence rate in the United States during 2003–2008 was 1.05 (95% CI: 1.03–1.06) cases per 100,000, with overall rates higher among men (rate = 1.93) compared to women (rate = 0.41). White males had the highest rate at 2.06/100,000 (Henley et al. 2013). Comparing these rates with those from 1991, the white male rate climbed by 0.36 per 100,000 while the female rate remained similar, around 0.4 per 100,000 (Ries et al. 1994). However, rates remained similar between men and women at ages below 45 years. From 45 years of age on, rates between men and women begin to

diverge, with the highest rates in the age group 75 years and older (Henley et al. 2013). A possible explanation for this divergence may be that disease patterns among the young are related to incidental or bystander exposures during their youth and not reflective of occupational exposures.

Overall, men displayed higher incidence of pleural mesothelioma, with 85% pleural and 7% peritoneal, compared to women, with 73% pleural and 18% peritoneal, which was significantly different (Henley et al. 2013). Significant differences were also noted by age groups, with the less than 45 years age group reporting 44% pleural as compared to peritoneal, rising to 77% pleural reported in the age group 45–54 years, to 85% pleural for those in the group 65 years of age or older (Henley et al. 2013). Incidence rates by state ranged from 0.58 to 1.65 per 100,000, and rates for women tended to be higher in those states where male rates were also high (Henley et al. 2013). Such findings are indicative of a similar etiology in both males and females. The correlation between pleural and peritoneal mesothelioma incidence within states during the years 2003–2008 was 0.7, while incidence rates reportedly decreased for men by 2.6% to approximately 2500 cases but remained steady among women, around 700 cases for each year between 2003 to 2008 (Henley et al. 2013).

In 2013, the latest year data from Centers for Disease Control and Prevention (CDC) database WONDER are reported, it is estimated there were 2,497 deaths<sup>3</sup> (1,911 males/586 females)<sup>4</sup> from mesothelioma in the United States based on death-certificate data coded from the ICD-10 code of C45.<sup>5</sup> Using this same data set, during 2003–2013, there were 29,776 mesothelioma deaths in the United States (CDC 2014). In the United States, it is estimated that approximately 1.3 million workers are exposed to asbestos, of the 125 million throughout the world (International Programme on Chemical Safety [IPCS] 2016). Currently, those most heavily exposed to asbestos in the United States are those in construction trades, which create exposure through demolition, remediation, and maintenance of homes, buildings, and schools still containing asbestos. Further, disaster-related asbestos exposures might affect large numbers of first responders—that is, firefighters, police, paramedics,

construction workers, and volunteers (Agency for Toxic Substances and Disease Registry [ATSDR] 2014). While background exposures exist in many parts globally, the cumulative risk from such background exposures is probably minor (Hillerdal 1999).

Mesothelioma is on the rise in many parts of the world, most likely due to the increased spread of asbestos usage over the past decades in developing countries. This has resulted in a corresponding shift of disease burden from the developed to developing countries (Delgermaa et al. 2011). Several studies demonstrated a linear relationship between historical asbestos use and mesothelioma incidence and mortality rates (Lin et al. 2007; Nishikawa et al. 2008; Tossavinen 2004). Mesothelioma was expected to produce 43,000 deaths globally annually (Driscoll et al. 2005). Delgermaa et al. (2011) noted 92,253 mesothelioma deaths from 83 countries during 1994–2008 and suggested that this may be an underestimate due to a variety of reporting errors and/or lack of data. Mesothelioma was found more accurately and frequently in developed countries, where better diagnosis and reporting occur. Developing countries are still in the early stages of perfecting the diagnosis of mesothelioma, and thus confounding occurs through misdiagnosis and/or reporting errors. Delgermaa et al. (2011) also observed that no global baseline was established to assess trends in mesothelioma, but that the rise of reported mesothelioma cases is likely due to better disease recognition as well as increasing incidence. In a recent analysis sponsored by the Gates Foundation, it is estimated that worldwide some 194,000 (range = 155,000 to 233,000) asbestos-related cancer deaths occurred in 2013, accounting for nearly two-thirds of the burden for all occupationally induced cancer, a 109.6% elevation since 1990, when 94,000 asbestos-related cancer deaths were estimated. In addition, the Gates Foundation report estimated some 3,402,000 disability-adjusted life-years lost (DALY), representing a 93.4% change since 1990. Mesothelioma accounted for approximately 50,400 (range = 44,200–57,600) cases estimated in the world for 2013, a significant change of 94.7% (range = 65.9–110.9) between 1990 to 2013 (GBD 2015a).

McDonald and McDonald (1996) estimated a background level of mesothelioma in the range of 1–2/million/year, while Hillerdal (1999) indicated that it is more likely less than 1/million/year. The mean age of death is around 70 years, with a global male-to-female ratio of 3.6:1 and anatomical site distribution of 41.3% pleura; 4.5% peritoneum; 0.3% pericardium; and 43.1% unspecified (Delgermaa et al. 2011). Using the CDC WONDER database, during 1999–2013 in the United States the anatomical site distribution was 7.1% pleural; 3.9% peritoneum; 0.1% pericardium; 11.7% other; and 77.2% unspecified (CDC 2014). While the WONDER database illustrates pleural as the most frequently reported location for mesothelioma, the largest number of deaths observed fell into the unspecified category, reflecting the well-recognized knowledge concerning unreliable nature of using only death-certificate analysis (Maudsley and Williams 1996).

### **Etiology of mesothelioma**

Mesothelioma originates from surface serosal cells of the pleural, peritoneal, and pericardial cavities (Pass et al. 2004), with a median survival of 7–12 months after diagnosis for its pleural form (MPM) (Panou et al. 2015; Sekido 2008). “How asbestos causes or contributes to mesothelioma development is still an enigma,” as is reconciling the diverse theories about the carcinogenic actions of the asbestos fibers during the long latent period associated with mesotheliomas (Pass et al. 2004).

Similar to other human cancers, malignant mesothelioma most likely develops via a multistep process, and not the malignant transformation of a mesothelial cell occurring soon after the initial asbestos exposure. Such an “initial hit” theory is unlikely, because mesothelioma has no detectable preinvasive phase and is a rapidly growing tumor, which points to multiple gene alterations following associated genetic and epigenetic events (Pass et al. 2004; Sekido 2008).

### **Plausible fiber actions in the human**

Several plausible explanations were suggested as to how asbestos fibers produce mesothelioma (Dodson 2011; Klebe and Henderson 2011; Pass et al. 2004; Robinson, Musk, and Lake 2005;

Sekido 2008). One mechanism involves mechanical irritation of the pleura by scratching the mesothelial surfaces, producing prolonged damage resulting in local irritation with cycles of repair. Second, asbestos fibers might interfere with the mitotic process of the cell cycle through disruption of the mitotic spindle, inducing chromosomal abnormalities and aneuploidy. Third, highly reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated by asbestos fibers, resulting in DNA damage and strand breaks. Finally, asbestos fibers might induce cytokines and growth factors, such as transforming growth factor- $\beta$  (TGF- $\beta$ ) and platelet-derived growth factor (PDGF), as well as transcription factors including nuclear factor kappa B (NF- $\kappa$ B) and activator protein-1 (AP-1). Brody (2010) further indicated that asbestos inhalation induced expression of TNF- $\alpha$  and TGF- $\beta$  at sites of fiber deposition in a dose-response manner with respect to gene expression *in situ*. Alveolar macrophages (AM) are an early hallmark of inhalation of asbestos because it was shown that these originate from activation of the fifth component of complement (C5a) through inhalation of asbestos fibers on the alveolar surfaces within minutes after the fibers are deposited (Brody 2010). Brody (2010) continued to explain that C5a is a potent chemoattractant for AM, enabling these cells to quickly accumulate where fibers deposit, and for mesothelioma suggested that the inflammatory cells that are close to the pleura might release growth factors that influence asbestos-induced mesothelial cell proliferation. The importance of the release of growth factors is that it is well established that dividing cells are more likely to undergo neoplastic transformation. Aust, Cook, and Dodson (2011) indicated that in mesothelioma, damage to cellular molecules or alteration in cellular processes that might involve a combination of the ability of asbestos to chemically generate potentially damaging reactive oxygen species (ROS) through surface iron (Fe) occurs. In addition, the interaction of the unique surfaces with cell membranes to trigger membrane receptor activation may take place.

IARC (2012) and Lemen and Dodson (2012) cited reports of mesothelioma molecular alterations found in the literature. The Institute of

Medicine (IOM 2006) reported that mineral fibers may directly induce genotoxicity through catalyzing the generation of ROS. Thus, both oxidized DNA bases and DNA strand breaks that were produced by asbestos exposures may induce gene mutation if not adequately repaired. Asbestos fibers have also physically interfered in the mitotic apparatus, resulting in aneuploidy (an unbalanced chromosome complement) or polyploidy (extra sets of chromosomes) and in specific chromosomal alterations characteristic of asbestos-induced cancer (Jaurand 1996). The suggested concept that Fe content of minerals was an important factor in the etiology of inducing mesothelioma (Crovella et al. 2016; Pascolo et al. 2013; Toyokuni 2011) is clearly brought into question when the fiber producing some of the highest rates of mesothelioma, erionite, is Fe free (IARC 1987; Metintas, Hillerdal, and Metintas 1999).

Pass et al. (2004) indicated smaller fibers are phagocytized and efficiently removed from the lung while larger fibers are not easily engulfed and usually only removed if solubilized. Amphiboles, unlike chrysotile, are not soluble and thus remain in the lung. Aust, Cook, and Dodson (2011) concluded that the potential for inhaled respirable elongated mineral particles (REMP), including asbestos, to induce irreversible cytopathological changes is the result of complex inherent features of fibrous dusts that are highly correlated with surface area of the fibers available for cellular contact. Brody (2010) indicated that all varieties of inhaled asbestos, including chrysotile, deposit initially along all aspects of the respiratory tract, and within the larger airways tend to accumulate at the bifurcations where many lung cancers appear to initiate. Brody (2010) further stated that at the alveolar level the bronchiolar-alveolar duct (BAD) junctions are the anatomical sites at which a majority of initial fibers deposit as a result of interception. The fibers are then translocated by Type 1 epithelium to underlying connective tissue spaces, where they injure the epithelium and activate fibrogenic growth factors that initiate asbestosis, while others of these fibers have access to the capillary bed and lymphatic flow in the lung interstitium, reaching the mesothelial surfaces of the pleura or peritoneum. Sekido (2008) noted that it is unclear whether asbestos fibers act directly on

the mesothelial cells or whether they indirectly mediate mesothelioma.

### ***Asbestos exposure concentrations***

Keeping these mechanistic issues in mind, then, how much exposure to asbestos does it take to induce the cellular process that leads to detectable disease? All asbestos-related diseases are dose/intensity dependent to some degree. Most exposures are to mixed dusts that may enhance asbestos effects (Aust, Cook, and Dodson 2011). It is also thought that overloading of the respiratory system might retard clearance and thus increase particle effect (Aust, Cook, and Dodson 2011). Langer and Nolan (1989) noted that mixtures of amphibole and chrysotile may be more potent as agents in the etiology of lung cancer and mesothelioma than just chrysotile alone. However, in the case of mesothelioma, in contrast to asbestosis, it appears that smaller doses are capable of producing the disease many years after exposure to asbestos. The first indications of this arose from observations by Wagner, Sleggs, and Marchard (1960), who described the potential exposures scenarios of 33 mesothelioma cases. In this case series, there were several who resided or worked near the mines with what could be considered lower exposures from those of the miners and millers of asbestos. Similar observations were subsequently made by Newhouse and Thompson (1965), who examined mesothelioma in the greater London (UK) area. Low exposures have continuously been reported in the scientific literature as causative of mesothelioma (Anderson et al., 1976; Hillerdal 1999; IARC 2012; National Institute for Occupational Safety and Health [NIOSH] 1995).

### ***Initial and subsequent exposures***

The question of which exposures contribute to an individual's mesothelioma cannot be answered through epidemiology alone. As Rothman and Greenland (2005) stated, "A cause of a disease event is an event, condition or characteristic that preceded the disease event and without which the disease event either would not have occurred at all or would not have occurred until some later time" (S144) Epidemiology indicates what occurs in a

population with similar characteristics, but cannot determine what happens within each individual of that population. Because mesothelioma is such a rare disease, its occurrence even in the highest asbestos-exposed populations is generally less than 10%. This calls into question the role of dose alone as the cause. Other factors need to be considered within an individual who eventually develops mesothelioma. What all of these factors are is still a mystery. Tomatis et al. (2007) found that most environmental carcinogens only produce cancer in about 10% of the exposed individuals, similar to the rate for asbestos-induced mesothelioma. Tomatis et al. (2007) presented evidence of individual susceptibility as playing a critical role; however, this is contradictory at present. Tomatis et al. (2007) disputed Chiappino's (2005) suggestion that there is a "trigger dose" of asbestos that is short-lasting and irreversible for causation because

Indeed, what is known about induction and growth of tumors strongly suggests that the progressive and irreversible development of the tumor cannot take place at the beginning of exposure or shortly thereafter. In fact, if models of time of reduplication of tumor cells—developed on the basis of studies carried out on this topic<sup>6</sup> (59–65)—are applied, for instance, to the period elapsing between the beginning of the exposure and the clinical manifestation of a case of mesothelioma with a latency of >10 years, the tumor mass would reach paradoxical dimensions. Therefore, "self-sufficiency" of the neoplastic process of the mesothelioma at the beginning of such a period of latency is hardly tenable. (Tomatis et al. 2007, p. 66)

Tomatis et al. (2007) concluded that if asbestos is a complete carcinogen, which is generally recognized to be the case, then it can both initiate and promote cancer. This indicates that the persistence of exposure after the initial exposure could not be discounted or irrelevant. Tomatis et al. (2007) cite Governa et al. (1999) to demonstrate that in vitro studies support the relevance of continuous inhalation of fibers in the etiology of mesothelioma.

A statement by the Collegium Ramazzini (CR) (2015a) indicated that "risk of malignant mesothelioma is related to cumulative exposure to asbestos in which all exposures—early as well as late—contribute to the totality of risk" (2). In making this conclusion the Collegium Ramazzini cites both the

Second Italian Consensus Conference on Pleural Mesothelioma and the Third Italian Conference on Malignant Mesothelioma of the Pleura, which noted that both intensity and duration of asbestos exposure are independent determinants of mesothelioma occurrence (Magnani et al. 2013, 2015).

The question is posed as to whether one fiber of asbestos initiates mesothelioma. This is a rather nonsensible question, because most exposed individuals have thousands to millions of asbestos fibers in their lungs and exposures do not occur to just one fiber at a time; rather, each exposure involves thousands or millions of asbestos-containing fibers. The majority of fibers inhaled never get past the body's own defense mechanisms to even reach the lower respiratory system (Newhouse, Sanchis, and Bienenstock 1976a, 1976b). Epidemiology demonstrated that an individual's risk of mesothelioma becomes greater as exposure to asbestos increases. However, as discussed earlier, even small exposures carry some risk for subsequent mesothelioma.

Therefore, is it really possible to say that the only and necessary cause of mesothelioma is transformation in a cell? What about the milieu in which the cell lives and divides? Is inflammation in the surrounding tissue a precondition to disease? Are there other external and internal factors that play a role in the etiology of mesothelioma? These are all questions asked by Seaton (2002) and are yet to be answered thoroughly in the etiology of mesothelioma. Obviously, each disease has an ultimate cause, and that ultimate cause may well be multiple factors coming together in the same individual in which the mesothelioma develops. While these questions cannot be answered with complete scientific validity, epidemiology does confirm the risk of developing mesothelioma is low in the absence of a history of exposure to asbestos. As stated earlier, mesothelioma is a "sentinel event," because it is most often associated with exposure to asbestos or some other elongated mineral particulate. Rudd, Moore-Gillon, and Muers (2002) suggested that it is clear the risk of mesothelioma rises in relation to dose of asbestos, although it is not possible to identify the particular fiber or group of fibers involved in the genesis of a specific mesothelioma.

Epidemiologically, it is appropriate to regard all sources of asbestos exposure as enhancing risk in the same way that all cigarettes smoked would be considered to have contributed to the risk of a lung cancer. In smoking-induced lung cancer, just like mesothelioma, there is a latency period before overt disease, and the amount of toxins inhaled during that period determines the overall risk. Thus, as with cigarettes and lung cancer, the dose of asbestos over time determines the risk for asbestos-induced mesothelioma.

The National Institute for Occupational Safety and Health Report for the United States Congress reviewed the available literature, including 12 epidemiology studies and multiple case reports, and concluded, "Mesothelioma has occurred following short term asbestos exposures of only a few weeks, and can result from very low levels of exposure" (NIOSH 1995 2015a). Hillerdal (1999) noted, after evaluating the epidemiological literature, that "There is no evidence of a threshold level below which there is no risk of mesothelioma. Low level exposure more often than not contains peak concentrations which can be very high for short periods." Hillerdal (1999, 505) also correlated exposure intensity and duration with latency, stating, "Latency time was also dependent on exposure, varying from 29.6 years for insulators (the highest exposure) to 51.7 in women with domestic exposure", (507) The International Mesothelioma Panel concluded: "The risk or incidence of mesothelioma shows a dose-response relation to cumulative asbestos exposure, so the risk is greatest with heavy exposures and that peritoneal mesothelioma are usually related to heavier cumulative exposures than pleural mesothelioma" (Galateau-Sallé 2006, 3).

Iwatsubo et al. (1998, 140) in their case-control epidemiology study noted, "We observed a dose-response relation with cumulative exposure from both intermittent and continuous patterns of exposure." This study further concluded, "Our results indicate that mesothelioma cases occurred below a cumulative exposure of 5 f/ml-years and perhaps below 0.5 f/ml years" (141) Rödelisperger et al. (2001, 262) reported: "Our results confirm the previously reported observation of a distinct dose-response relationship, even at levels of cumulative exposure below 1 fiber year." This finding is

clearly in support of the outcome of the French mesothelioma case-control study by Iwatsubo et al. (1998). Sporn, and Roggli (2004, 107) observed, “There is a linear dose-response relationship between the amount of asbestos to which an individual is exposed and the risk of developing mesothelioma. In addition, a threshold level of exposure below which mesothelioma will not occur has not yet been identified.” Battifora and McCaughey (1995), of the Armed Forces Institute of Pathology, indicated, “The incidence of diffuse malignant mesothelioma rises with increasing intensity and duration of exposure to asbestos; the dose-specific risk data is a linear relationship.” Further, the U.S. Consumer Product Safety Commission (1997) “noted that in the scientific literature there is general agreement that there is no known threshold level below which exposure to respirable free-form asbestos would be considered safe.”

Selikoff and Lee (1978, 273) stated: “One would expect the onset of mesothelioma to occur earlier and more frequently in those exposed to doses that are high but insufficient to incite serious competition from parenchymal fibrosis.” Churg and Green (1998, 350) agreed with the Selikoff and Lee (1978) prediction on how dose affects latency “as exposure level decreases, the latency period increases.” In contrast, the III Italian Consensus Conference on Mesothelioma of the Pleura in 2015 concluded: “Under the expectation of a shorter latency for the most exposed, it is fallacious because its results do not depend on the relationship between exposure and disease, but on the time boundaries of the observation,” suggesting “the average latency is unaffected.” However, this conclusion was not unanimous, because “Claudio Bianchi believes that an inverse relationship exists between intensity of asbestos exposure and length of the latency period” (Magnani et al. 2015, 329). Even though there may be some controversy regarding exposure effect on latency, the conference found general support “that duration and intensity are independent determinants of MM occurrence.” (Magnani et al. 2015, 329).

Bignon et al. (2002, 37), after reviewing multiple studies, found “that each exposure parameter contributed to some extent to the mesothelioma.” These exposure parameters included probability

of exposure, intensity, and frequency. Bignon et al. (2002) noted that when these three parameters and duration of exposure were fitted together and summed over an entire working life, the OR increased from (OR = 1.2; 95% CI 0.8–1.8) in the lowest exposure category to (OR = 8.7; 95% CI 4.1–18.5) in the highest. Taking into account Albin et al. (1990), Bignon et al. (2002) noted that the cumulative exposure elevated the RR by 1.9 for each 1 f/mL-year among employees with 40 years or more exposure. Newhouse, Berry, and Wagner (1985) in their study among factory workers found mesothelioma death rates rose according to both duration and severity of asbestos exposure, while Raffn et al. (1989) reported pleural mesothelioma increasing with duration of exposure among subjects having 15 or more years of latency (SIR = 3.77 for less than 5 years of exposure versus an SIR = 13.56 for more than 5 years of exposure). Peto, Seidman, and Selikoff (1982), when examining an insulator cohort from North America by utilizing mathematical modeling, found the third or fourth power of time since first exposure were best compatible with a linear dose-response relationship.

Bignon et al. (2002, 37) noted “These results suggest that each exposure parameter contribute to some extent to the mesothelioma, although the dose-response relationship seemed to be described best by the CEI.”<sup>7</sup> Further, Bignon et al. (2002, 37) wrote that while “very few studies have focused on the time-related pattern of occupational exposure as a significant factor in the occurrence of mesothelioma. Our study examined the temporal exposure pattern according to the frequency of exposure and the CEI. We observed a dose-response relationship with cumulative exposure for both intermittent and continuous pattern of exposure.” Evidence indicated “Our results suggested that intermittent exposure does not carry as high a risk as continuous exposures.”

Peto et al. (2009, 45) reported:

If this apparent synergistic interaction between early and later exposures is real, the conventional additive model proposed almost 30 years ago (Peto 1978) on which risk assessments (HEI, 1991) and recent predictions of mesothelioma incidence (Hodgson et al. 2005) were based should be modified. Under this additive model most cases are caused by exposures

at younger ages and the additional effect of later exposure is much less.

Contrary to prevailing thought that latency, frequency, and intensity are key factors in determining subsequent risk, La Vecchia and Boffetta (2011) argue that only latency is key and that mesothelioma risk is not influenced by later exposures in life. However, their reasoning suffers from several key flaws, including a selective review of the literature with their conclusions not supported by the original results of the studies included in their review (Terracini et al. 2014). La Vecchia and Boffetta (2011) also use SMR for comparing studies which are not mutually standardized, making any comparisons questionable because using such SMR may allow influence from a variety of other factors, including age, to bias the results. Their analysis also ignores differences or changes in exposure patterns, which are important. For example, asbestos exposures may have been markedly lower in later time periods for workers with long duration of exposure, that is, after age 30 years. In addition, by not accounting for exposure over time the investigators failed to address effects from cumulative exposures. Further, as noted by Terracini et al. (2014), by lumping together pleural and peritoneal cancers, differences in both dose-effect and time-effect relationships of the two types of mesothelioma were ignored. Finally, the CI for all the RR are so large that this calls into question their meaning. Although the CI overlap in all the tables presented, Terracini et al. (2014) continued to interpret these relationships to fit their conclusion. The Collegium Ramazzini (2015a, 2), after reviewing the entirety of scientific data, concluded that the “risk of malignant mesothelioma is related to cumulative exposure to asbestos in which all exposures—early as well as late—contribute to the totality of risk.”

## Conclusions

Mesothelioma, a rare tumor, is most often highly correlated with asbestos exposure. Many of the same factors related to asbestos may be relevant in the etiology of mesothelioma induced from other respirable elongated mineral particles (REMP), including mineral type, physical features of inhalation, and surface chemical composition (Aust, Cook, and Dodson

2011). To date, science has not been able to define an exposure from asbestos fibers below which there is not some cancer risk. This is likely due to unknown factors in genetic susceptibility. Mesothelioma, like all asbestos-related diseases, is dose/intensity dependent to some degree, and studies showed that as cumulative exposures rise, so does risk. Multiple processes take place in an individual before the disease mesothelioma manifests itself, and just as with lung cancers attributed to cigarette smoking, it cannot be determined with any degree of certainty which particular asbestos exposure contributed to an individual's mesothelioma. Thus, as NIOSH concluded in 1976, when recommending a revised asbestos standard of 100,000 fibers  $>5 \mu\text{m length/m}^3$  to protect against the noncarcinogenic effects of asbestos and to materially reduce the risk of asbestos-induced cancer, “only a ban can assure protection against carcinogenic effects of asbestos” (NIOSH 1976, 93). This investigation continues to support such an approach for the elimination of asbestos-induced mesotheliomas.

## Disclaimer

Dr. Lemen has testified on behalf of plaintiffs in asbestos litigation.

## Notes

1. All SMRs had 95% confidence intervals (CIs) that did not include 100.
2. SEER is the Surveillance, Epidemiology, and End Results, Program of the National Cancer Institute, and is a source of information on cancer incidence and survival in the United States. Case ascertainment began on January 1, 1973, in the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii and the metropolitan areas of Detroit and San Francisco–Oakland. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 28% of the U.S. population.
3. Deaths based on underlying cause of death.
4. Ratio for male to female = 3.3:1.
5. Crude rate per 100,000 for males = 1.2(95% CI: 1.2–1.3); females = 0.4(5% CI: 0.3–0.4); and the age-adjusted rate per 100,000 for males = 1.3(95%CI: 1.2–1.3); females 0.3(95% CI: 0.3–0.3).
6. (59–65) refers to: Collins, Loeffler, and Tivey (1956); Tannock (1983); Flora and Vannucci (1996); Cotran, Kumar, and Collins (1999); Bregni et al. (2000).
7. CEI, cumulative exposure index.

## Notes on contributor

Richard Lemen is a retired former Assistant Surgeon General of the United States Public Health Service and Deputy Director and Acting Director of the National Institute for Occupational Safety and Health. He also serves as a Presidential Appointee to the United States Presidential Advisory Board on Radiation and Worker Health, 2009–present.

## References

- Agency for Toxic Substance & Disease Registry. 2014. Asbestos toxicity: Who is at risk of exposure to asbestos? Atlanta, GA: Agency for Toxic Substance & Disease Registry, Centers for Disease Control and Prevention. August.
- Albin, M., K. Jakobsson, R. Attewell, L. Johansson, and H. Welinder. 1990. Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. *British Journal of Industrial Medicine* 47:602–10.
- Anderson, H. A., R. Lilis, S. M. Daum, A. S. Fischbein, and I. J. Selikoff. 1976. Household –contact asbestos neoplastic risk. In *Occupational carcinogenesis*, ed. U. Saffiotti and J. K. Wagoner, *Annals of the New York Academy of Sciences* 271: 311–23.
- Ascoli, V., D. Cavone, E. Merler, P. G. Barbieri, L. Romeo, F. Nardi, and M. Musti. 2007. Mesothelioma in blood related subjects: Report of 11 clusters among 1954 Italy cases and review of the literature. *American Journal of Industrial Medicine* 50:357–69. doi:10.1002/(ISSN)1097-0274.
- Ascoli, V., C. Mecucci, and S. Knuutila. 2001. Genetic susceptibility and familial malignant mesothelioma–Correspondence. *Lancet* 357:1804. doi:10.1016/S0140-6736(00)04922-9.
- Ascoli, V., E. Romeo, C. Carnovale Scalzo, I. Cozzi, L. Ancona, F. Cavariani, A. Balestri, L. Gasperini, and F. Forastiere. 2014. Familial malignant mesothelioma: A population-based study in central Italy (1980–2012). *Cancer Epidemiology* 38:273–78. doi:10.1016/j.canep.2014.02.014.
- Aust, A. E., P. M. Cook, and R. F. Dodson. 2011. Morphological and chemical mechanisms of elongated mineral particle toxicities. *Journal of Toxicology and Environmental Health, Part B* 14:40–75. doi:10.1080/10937404.2011.556046.
- Barbieri, P. G., M. Migliori, and E. Merier. 1999. Incidence of malignant mesothelioma and occupational asbestos exposure in Northern Italy. *La Medicina del Lavoro* 90:762–75.
- Baris, I., M. Artvinli, A. Sahin, T. Savas, and M. L. Erkan. 1979. Study of malignant pleural mesothelioma, chronic fibrotic pleurisy and pleural plaques related to the environment in Turkey. *Revue des Maladies Respiratoires* 7:687–94.
- Battifora, H., and W. T. E. McCaughey. 1995. Tumours of the serosal membranes. In *Atlas of tumour pathology*, third series, fascicle, 15. Washington, DC: Universities Associated for Research & Education in Pathology, Inc., Armed Forces Institute Pathology.
- Betti, M., E. Casalone, D. Ferrante, A. Romanelli, F. Grosso, S. Guarrera, L. Righi, S. Vatrano, G. Pelosi, R. Libener, D. Mirabelli, R. Boldorini, C. Casadio, M. Papotti, G. Matullo, C. Magnani, and I. Dianzan. 2015. Inference on germline BAP1 mutations and asbestos exposure from the analysis of familial and sporadic mesothelioma in a high-risk area. *Genes, Chromosomes and Cancer* 54:51–62. doi:10.1002/gcc.v54.1.
- Bignon J, Y. Iwatsubo, F. Galateau-Salle, and A. J. Valleron. 2002. History and experience of mesothelioma in Europe. In *Mesothelioma*, ed. B. W.S. Robinson and A. P. Chahinian, 29–53. London, UK: Martin Dunitz Ltd., Taylor & Francis Group.
- Bregni M, S. Siena, G. Bonadonna. 2000. Principi di Proliferazione cellulare. In *Medicina oncologica*, ed. G. Bonadonna, G. Robustelli, and M. della Cuna, 73–115. Milano, Italy: Masson [in Italian].
- Brody, A. R. 2010. Editorial asbestos and lung disease. *American Journal of Respiratory Cell and Molecular Biology* 42:131–32. doi:10.1165/rcmb.2010-2002ED.
- Camus, M., J. Siemiatycki, and G. Meek. 1998. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. *New England Journal of Medicine* 338:1565–71. doi:10.1056/NEJM199805283382201.
- Carbone, M., I. Baris, P. Bertino, B. Brass, S. Comertpay, A. U. Dogan, G. Gaudino, S. Jube, S. Kanodia, C. R. Partridge, H. I. Pass, A. S. Rivera, I. Steele, M. Tuncer, S. Way, H. Yang, and A. Miller. 2011. Erionite exposure in North Dakota and Turkish villages with mesothelioma. *Proceedings of the National Academy of Sciences* 108:13618–23. doi:10.1073/pnas.1105887108.
- Carbone, M., S. Emri, A. U. Dogan, I. Steele, M. Tuncer, H. I. Pass, and Y. I. Baris. 2007. A mesothelioma epidemic in cappadocia: Scientific developments and unexpected social outcomes. *Nature Reviews, Cancer* 7:147–54. doi:10.1038/nrc2068.
- CDC. 2014. Compressed mortality file 1999–2013 on CDC WONDER Online Database for Mesothelioma (C45: ICD-10). Centers for Disease Control and Prevention, National Center for Health Statistics. October 30. Compressed Mortality File 1999-2013 Series 20, No. 25. <http://wonder.cde.gov/cmfile-icd10.html>.
- Checkoway, H., N. E. Pearce, and D. J. Crawford-Brown. 1989. *Research methods in occupational epidemiology*. New York, NY: Oxford University Press.
- Cheung, M., Y. Kadaniya, J. Talarchek, J. Pei, J. A. Ohar, O. R. Kayalah, and J. R. Testa. 2016. Germline BAP1 mutation in a family with high incidence of multiple primary cancers and a potential gene–environment interaction. *Cancer Letters* 76:206–15.
- Cheung, M., Y. Kadariya, J. Pei, J. Talarchek, F. Facciolo, P. Visca, L. Righi, I. Cozzi, J. R. Testa, and V. Ascoli. 2015. An asbestos-exposed family with multiple cases of pleural malignant mesothelioma without inheritance of a predisposing BAP1 mutation. *Cancer Genetics* 208:502–7. doi:10.1016/j.cancergen.2015.07.004.
- Chiappino, G. 2005. Mesothelioma: Il ruolo delle fibre ultra-fine e conseguenti riflessi in campo preventive e medicolegale. *La Medicina del Lavoro* 96:3–23 [in Italian].
- Churg, A., and F. H. Y. Green. 1998. *Pathology of occupational lung disease*, 2nd ed. Baltimore, MD: Williams & Wilkins.

- Collegium Ramazzini. 2015a. Comments on the causation of malignant mesothelioma: Rebutting the false concept that recent exposures to asbestos do not contribute to causation of mesothelioma. Carpi, Italy. [http://www.collegiumramazzini.org/download/18\\_EighteenthCRStatement](http://www.collegiumramazzini.org/download/18_EighteenthCRStatement) (accessed October 14, 2015).
- Collegium Ramazzini. 2015b. The global health dimensions of asbestos and asbestos-related diseases. Collegium Ramazzini, Carpi, Italy, [http://www.collegiumramazzini.org/download/18\\_EighteenthCRStatement](http://www.collegiumramazzini.org/download/18_EighteenthCRStatement) (accessed October 14).
- Collins, V. P., R. K. Loeffler, and H. Tivey. 1956. Observations on growth rates of human tumours. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* 76:988.
- Cotran, R. S., V. Kumar, and T. Collins. 1999. Neoplasia. In *Robbins pathologic basis of disease*, ed. R. S. Cotran, V. Kumar, and S. L. Robbins, 300–1. Philadelphia, PA: W. B. Saunders.
- CR (Consensus Report). 1997. Asbestos, asbestosis, and cancer: The Helsinki criteria for diagnosis and attribution. *Scandinavian Journal of Work, Environment & Health* 23:311–16.
- Crovella, S., A. M. Bianco, J. Vuch, L. Zupin, R. R. Moura, E. Trevisan, M. Schneider, A. Brollo, E. M. Nicastro, A. Coszeni, G. Zabucchi, and V. Borelli. 2016. Iron signature in asbestos-induced malignant pleural mesothelioma: A population-based autopsy study. *Journal of Toxicology and Environmental Health, Part A* 79:129–41. doi:10.1080/15287394.2015.1123452.
- Cyphert, J. M., D. J. Carlin, A. Nysak, M. C. Schladweiler, A. D. Ledbetter, J. H. Shannahan, U. P. Kodavanti, and S. H. Gavett. 2015. Comparative long-term toxicity of Libby amphibole and amosite asbestos in rats after single or multiple intratracheal exposures. *Journal of Toxicology and Environmental Health, Part A* 78:151–65. doi:10.1080/15287394.2014.947455.
- Delgermaa, V., K. Takahashi, E.-K. Park, G. V. Le, H. Toshiyuki, and T. Sorahan. 2011. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. *Bulletin of the World Health Organization* 89:716C–724C. doi:10.2471/BLT.11.086678.
- Dodson, R. F. 2011. Analysis and relevance of asbestos burden in tissue. In *Asbestos risk assessment, epidemiology, and health effects*, ed. R. F. Dodson and S. P. Hammar, 49–108. 2nd ed. Bacon Raton, FL: CRC Press, Taylor & Francis Group.
- Dragon, J., J. Thompson, M. MacPherson, and A. Shukla. 2015. Differential susceptibility of human pleural and peritoneal mesothelial cells to asbestos exposure. *Journal of Cellular Biochemistry* 116:1540–52. doi:10.1002/jcb.v116.8.
- Driscoll, T., D. I. Nelson, K. Steenland, J. Leigh, M. Concha-Barrientos, M. Fingerhut, and A. Prüss-Ustün. 2005. The global burden of disease due to occupational carcinogens. *American Journal of Industrial Medicine* 48:419–31. doi:10.1002/(ISSN)1097-0274.
- Flora, S., and A. Vannucci. 1996. *La prevenzione primaria dei tumori*. Professione: Sanità Pubblica e Medicina Pratica. Roma, Italy.
- Galateau-Sallé, F., ed. 2006. *Pathology of malignant mesothelioma. international mesothelioma panel*. London, UK: Springer – Verlag.
- Global Burden of Disease. 2015a. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 1888 countries, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 386:743–800. doi:10.1016/S0140-6736(15)60692-4.
- Governa, M., M. Amati, S. Fontana, I. Visona, G. C. Botta, F. Mollo, D. Bellis, and P. Bo. 1999. Role of iron in asbestos-body-induced oxidant radical generation. *Journal of Toxicology and Environmental Health. Part A* 58:279–87. doi:10.1080/009841099157241.
- Health Effects Institute. 1991. *Asbestos in public and commercial buildings: A literature review and synthesis of current knowledge*. Cambridge, MA: Health Effects Institute—Asbestos Research.
- Henderson, D. W., K. B. Shilkin, and S. L. P. Langlois, Whitaker, D. 1992. *Malignant mesothelioma*. New York, NY: Hemisphere.
- Henley, S. J., T. C. Larson, M. Wu, C. S. A. Vinicius, M. Lewis, G. A. Pinheiro, and C. Ehemann. 2013. Mesothelioma incidence in 50 states and the District of Columbia, United States, 2003–2008. *International Journal of Occupational and Environmental Health* 19:1–10. doi:10.1179/2049396712Y.0000000016.
- Hillerdal, G. 1999. Mesothelioma: Cases associated with non-occupational and low dose exposures. *Occupational and Environmental Medicine* 56:505–13. doi:10.1136/oem.56.8.505.
- Hodgson, J. T., D. M. Elvenny, A. J. Darnton, M. J. Price, and J. Peto. 2005. The expected burden of mesothelioma mortality in Great Britain from 2002 to 2050. *British Journal of Cancer* 92:587–93.
- IARC. 1987. Erionite. In *Silica and some silicates*, IARC monogr. Eval. Carcinogen. Risk Chem. Hum. 42:225–39.
- IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2012. *A review of human carcinogens, part C: Arsenic, metals, fibres, and dusts*, vol. 100. Lyon, France: Published by the International Agency for Research on Cancer, World Health Organization.
- Institute of Medicine. 2006. *Asbestos: Selected cancers*. Washington, DC: Institute of Medicine of the National Academies, The National Academies Press.
- International Programme on Chemical Safety. 1998. Environmental Health Criteria 203—Chrysotile asbestos. International Programme on Chemical Safety, United Nations Environment Programme, The International Labour Organisation, and the World Health Organization, Geneva; WHO. Occupational Exposure limit for asbestos, WHO/OCH/89. I. Office of Occupational Health. Geneva, Switzerland: World Health Organization.

- International Programme on Chemical Safety. 2016. Asbestos. [http://www.who.int/ipcs/assessment/public\\_health/asbestos/en/](http://www.who.int/ipcs/assessment/public_health/asbestos/en/).
- Iwatsubo, Y., J. C. Pairon, C. Boutin, O. Menard, N. Massin, D. Caillaud, E. Orlowald, F. Galateau-Sallé, J. Bignon, and P. Brochard. 1998. Pleural mesothelioma: Dose-response relation at low levels of asbestos exposure in a French population-based case-control study. *American Journal of Epidemiology* 148:133–42. doi:10.1093/oxfordjournals.aje.a009616.
- Jaurand, M. C. 1996. Use of in-vitro genotoxicity and cell transformation assays to evaluate the potential carcinogenicity of fibres. IARC SciIOM Publication 55–72, PMID-9101317, Lyon, France.
- Jones, R. D., D. M. Smith, and P. G. Thomas. 1988. Mesothelioma in Great Britain in 1968–1983. *Scandinavian Journal of Work, Environment & Health* 14:145–52. doi:10.5271/sjweh.1938.
- Klebe, S., and D. W. Henderson. 2011. The molecular pathogenesis of asbestos-related disorders. In *Asbestos risk assessment, epidemiology, and health effects*, 2nd ed., ed. R. F. Dodson and S. P. Hammar, 109–30. Bacon Raton, FL: CRC Press, Taylor & Francis Group.
- Krupoves, A., M. Camus, and L. De Guire. 2015. Incidence of malignant mesothelioma of the pleura in Québec and Canada from 1984 to 2007, and projections from 2008 to 2032. *American Journal of Industrial Medicine* 58:473–82. doi:10.1002/ajim.22442.
- La Vecchia, C., and P. Boffetta. 2011. Role of stopping exposure and recent exposure to asbestos in the risk of mesothelioma. *European Journal of Cancer Prevention* 21:227–30. doi:10.1097/CEJ.0b013e32834dbc56.
- Langer, A. M., and R. P. Nolan. 1989. Fibre type and burden in parenchymal tissues of workers occupationally exposed to asbestos in the United States. In *Non-occupational exposures to mineral fibres*, ed. J. Bignon, J. Peto, and R. Saracci, 330–35. IARC Sci. Pub. no. 90. Lyon, France: International Agency for Research on Cancer, World Health Organization.
- Larson, T., N. Melnikova, S. I. Davis, and P. Jamison. 2007. Incidence and descriptive epidemiology of mesothelioma in the United States, 1999–2002. *International Journal of Occupational and Environmental Health* 13:398–403. doi:10.1179/oeh.2007.13.4.398.
- Leigh, J., P. Davidson, L. Hendrie, and D. Berry. 2002. Malignant mesothelioma in Australia 1945–2000. *Annals of Occupational Hygiene* 46 (Suppl. 1):160–65. doi:10.1093/annhyg/46.suppl\_1.160.
- Lemen, R. 2014. Epidemic to pandemic: Asbestos in our world. In *International day of asbestos victims—State of science—State of the world*, 3–33. Marc Hindry, Paris, France: Andeva, Association Nationale de Défense des Victimes de l'Amiante.
- Lemen, R. A. 2011. Epidemiology of asbestos-related diseases and the knowledge that led to what is known today. In *Asbestos risk assessment, epidemiology, and health effects*, ed. R. F. Dodson and S. P. Hammar, 132–267. 2nd ed. Bacon Raton, FL: (CRC Press, Taylor & Francis Group.
- Lemen, R. A., and R. F. Dodson. 2012. Asbestos. In *Patty's toxicology*, 6th ed., ed. E. Bingham and B. Cohns, vol. 5, chap. 83. Hoboken, NJ: John Wiley & Sons, Inc.
- Lin, R. T., K. Takahashi, A. Karjalainen, T. Hoshuyama, D. Wilson, and T. Kameda. 2007. Ecological association between asbestos-related diseases and historical asbestos consumption: An international analysis. *Lancet* 369: 844–49. doi:10.1016/S0140-6736(07)60412-7.
- Linton, A., J. Vardy, S. Clarke, and N. Van Zandwijk. 2012. The ticking time-bomb of asbestos: Its insidious role in the development of malignant mesothelioma. *Critical Reviews in Oncology/Hematology* 84:200–12. doi:10.1016/j.critrevonc.2012.03.001.
- Lunder, S. 2015. *Asbestos nation*. Washington, DC: Environmental Working Group.
- Magnani, C., C. Bianchi, E. Chellini, D. Consonni, B. Fubini, V. Gennaro, A. Marinaccio, M. Menegozzo, D. Mirabelli, E. Merler, F. Merletti, M. Musti, E. Oddone, A. Romanelli, B. Terracini, A. Zona, C. Zocchetti, M. Alessi, A. Baldassarre, I. Dianzani, M. Maule, C. Mensi, and S. Silvestri. 2015. III Italian consensus conference on malignant mesothelioma of the pleura. Epidemiology, public health and occupational medicine related issues. *La Medicina del Lavoro* 106:325–32.
- Magnani, C., B. Fubini, D. Mirabelli, C. Bianchi, E. Chellini, V. Gennaro, A. Marinaccio, M. Menegozzo, E. Merler, F. Merletti, M. Musti, E. Pira, A. Romanelli, B. Terracini, and A. Zona. 2013. Pleural mesothelioma: Epidemiological and public health issues. Report from the second Italian consensus conference on pleural mesothelioma. *La Medicina del Lavoro* 104:191–202.
- Marinaccio, A., A. Binazzi, M. Bonafede, M. Corfiati, D. Di Marzio, A. Scarselli, M. Verardo, D. Mirabelli, V. Gennaro, C. Mensi, G. Schallemborg, E. Merler, C. Negro, A. Romanelli, E. Chellini, S. Silvestri, M. Cocchioni, C. Pascucci, F. Stracci, V. Ascoli, L. Trafficante, I. Angelillo, M. Musti, D. Cavone, G. Cauzillo, F. Tallarigo, R. Tumino, and M. Melis; ReNaM Working Group. 2015. Malignant mesothelioma due to non-occupational asbestos exposure from the Italian national surveillance system (ReNaM): Epidemiology and public health issues. *Occupational and Environmental Medicine* 72:648–55. doi:10.1136/oemed-2014-102297.
- Mark, E. J., and T. Yokoi. 1991. Absence of evidence for a significant background incidence of diffuse malignant mesothelioma apart from asbestos exposure. *Annals of the New York Academy of Sciences* 643:196–204. doi:10.1111/nyas.1991.643.issue-1.
- Markowitz, S. 2015. Asbestos-related lung cancer and malignant mesothelioma of the pleura: Selected current issues. *Seminars in Respiratory and Critical Care Medicine* 36:334–46. doi:10.1055/s-00000075.
- Maudsley, G., and E. M. I. Williams. 1996. Inaccuracy in death certification—Where are we now? *Journal of Public Health* 18:59–66. doi:10.1093/oxfordjournals.pubmed.a024463.
- McDonald, A. D. 1980. Malignant mesothelioma in Quebec. In *Biological effects of mineral fibres*, 673–80. IARC

- Scientific Publication No. 30. J.D. Wagner, Lyon, France: International Agency for Research on Cancer.
- McDonald, J. C., and A. D. McDonald. 1996. The epidemiology of mesothelioma in historical context. *European Respiratory Journal* 9:1932–42. doi:10.1183/09031936.96.09091932.
- Metintas, M., G. Hillerdal, and S. Metintas. 1999. Malignant mesothelioma due to environmental exposure to erionite: Follow-up of a Turkish emigrant cohort. *European Respiratory Journal* 13:523–26. doi:10.1183/09031936.99.13352399.
- Mullan, R. J., and L. I. Murthy. 1991. Occupational sentinel health events: An up- dated list for physicians recognition and public health surveillance. *American Journal of Industrial Medicine* 19:775–79. doi:10.1002/(ISSN)1097-0274.
- National Institute for Occupational Safety and Health. 1976. *Revised recommended asbestos standard*. Cincinnati, Ohio: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health.
- National Institute for Occupational Safety and Health. 1995. *Report to congress on workers' home contamination study conducted under The Workers' Family Protection Act (29 U.S.C. 671a)*. Cincinnati, Ohio: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.
- Neumann, V., A. Rütten, M. Scharmach, K.-M. Müller, and M. Fischer. 2004. Factors influencing long-term survival in mesothelioma patients – Results of the German mesothelioma register. *International Archives of Occupational and Environmental Health* 77:191–99. doi:10.1007/s00420-003-0498-6.
- Newhouse, M., J. Sanchis, and J. Bienenstock. 1976a. Lung defense mechanisms (first of two parts). *New England Journal of Medicine* 295:990–98. doi:10.1056/NEJM197610282951805.
- Newhouse, M., J. Sanchis, and J. Bienenstock. 1976b. Lung defense mechanisms (second of two parts). *New England Journal of Medicine* 295:1045–52. doi:10.1056/NEJM197611042951905.
- Newhouse, M. L., and G. Berry. 1976. Predictions of mortality from mesothelial tumours in asbestos factory workers. *British Journal of Industrial Medicine* 33:147–51.
- Newhouse, M. L., and G. Berry. 1979. Patterns of mortality in asbestos factory workers in London. *Annals of the New York Academy of Sciences* 330:53–60. doi:10.1111/nyas.1979.330.issue-1.
- Newhouse, M. L., G. Berry, and J. C. Wagner. 1985. Mortality of factory workers in east London 1933–80. *British Journal of Industrial Medicine* 42:4–11.
- Newhouse, M. L., and H. Thompson. 1965. Mesothelioma of pleura and peritoneum following exposure to asbestos in the London area. *British Journal of Industrial Medicine* 22:261–69.
- Nicholson, W. J. 2001. The carcinogenicity of chrysotile asbestos—A review. *Industrial Health* 39:57–64. doi:10.2486/indhealth.39.57.
- Nishikawa, K., K. Takahashi, A. Karjalainen, C.-P. Wen, S. Furuya, T. Hoshuyama, M. Todoroki, Y. Kiyomoto, D. Wilson, T. Higashi, M. Ohtaki, G. Pan, and G. Wagner. 2008. Recent mortality from pleural mesothelioma, historical patterns of asbestos use and adoption of bans: A global assessment. *Environmental Health Perspectives* 116:1675–80. doi:10.1289/ehp.11272.
- Panou, V., M. Vyberg, U. M. Weinreich, C. Meristoudis, U. G. Falkmer, and O. D. Røe. 2015. The established and future biomarkers of malignant pleural mesothelioma. *Cancer Treatment Reviews* 41:486–95. doi:10.1016/j.ctrv.2015.05.001.
- Pascolo, L., A. Gianoncelli, G. Schneider, M. Salomé, M. Schneider, C. Calligaro, M. Kiskinova, M. Melato, and C. Rizzardì. 2013. The interaction of asbestos and iron in lung tissue revealed by synchrotron-based scanning x-ray microscopy. *Scientific Reports* 3:1123.
- Pass, H. I., N. Vogelzang, S. Hahn, and M. Carbone. 2004. Malignant pleural mesothelioma. *Current Problems in Cancer* 28:93–174. doi:10.1016/j.currproblcancer.2004.04.001.
- Peto, J. 1978. The hygiene standard for chrysotile asbestos. *Lancet* 311:484–89. doi:10.1016/S0140-6736(78)90145-9.
- Peto, J., C. Rake, C. Gilham, and J. Hatch. 2009. Occupational, domestic and environmental mesothelioma risks in Britain: A case-control study. Prepared by the Institute of Cancer Research and the London School of Hygiene and Tropical Medicine for the Health and Safety Executive, Health and Safety Executive, London, UK.
- Peto, J., H. Seidman, and I. J. Selikoff. 1982. Mesothelioma mortality in asbestos workers: Implications for models of carcinogenesis and risk assessment. *British Journal of Cancer* 45:124–35. doi:10.1038/bjc.1982.15.
- Pinheiro, G. A., V. C. S. Antao, K. M. Bang, and M. D. Attfield. 2004. Malignant mesothelioma surveillance: A comparison of ICD 10 mortality data with SEER incidence data in nine areas of the United States. *International Journal of Occupational and Environmental Health* 10:251–55. doi:10.1179/oeh.2004.10.3.251.
- Pinton, G., E. Brunelli, B. Murer, R. Puntoni, M. Puntoni, D. A. Fennell, G. Gaudino, L. Mutti, and L. Moro. 2009. Estrogen receptor-beta affects the prognosis of human malignant mesothelioma. *Cancer Research* 69:4598–604. doi:10.1158/0008-5472.CAN-08-4523.
- Pira, E., C. Pelucchi, L. Buffoni, A. Palmas, M. Turbiglio, E. Negri, P. G. Piolatto, and C. La Vecchia. 2005. Cancer mortality in a cohort of asbestos textile workers. *British Journal of Cancer* 92:580–86. doi:10.1038/sj.bjc.6602240.
- Raffin, E., E. Lynge, K. Juel, and B. Korsgaard. 1989. Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. *British Journal of Industrial Medicine* 46:90–96.
- Reid, A., N. H. De Klerk, C. Magnani, D. Ferrante, G. Berry, A. W. Musk, and E. Merier. 2014. Mesothelioma risk after 40 years since first exposure to asbestos: A pooled analysis. *Thorax* 69:107–12. doi:10.1136/thoraxjnl-2013-204161.
- Ries, L. A. G., B. A. Miller, B. F. Hankey, C. Kosary, A. Hargraves, and B. Edwards, eds. 1994. *SEER cancer statistics*

- review, 1973–1991, *Tables and graphs*. Bethesda, MD: National Cancer Institute. (NIH Publication no 94-2789).
- Robinson, B. W., A. W. Musk, and R. A. Lake. 2005. Malignant mesothelioma. *The Lancet* 366:397–408. doi:10.1016/S0140-6736(05)67025-0.
- Robinson, B. W. S., and A. P. Chahinian, eds. 2002. *Mesothelioma*. London, UK: Martin Dunitz Ltd., Taylor & Francis Group.
- Rödelsperger, K., J. K-H, H. Pohlabein, W. Römer, and H. J. Woitowitz. 2001. Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: Results from a German hospital-based case-control study. *American Journal of Industrial Medicine* 39:262–75. doi:10.1002/1097-0274(200103)39:3<262::AID-AJIM1014>3.0.CO;2-R.
- Röesler, J. A., H. J. Woitowitz, H.-J. Lange, R. H. Woitowitz, K. Ulm, and K. Rödelsperger. 1994. Mortality rates in a female cohort following asbestos exposure in Germany. *Journal of Occupational Medicine* 36:889–93.
- Rothman, K. J., and S. Greenland. 2005. Causation and causal inference in epidemiology. *American Journal of Public Health* 95 (Supp 1):S144–S150. doi:10.2105/AJPH.2004.059204.
- Roushdy-Hammod, I., J. Siegel, S. Emri, J. R. Testa, and M. Carbone. 2001. Genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. *Lancet* 357:444–45. doi:10.1016/S0140-6736(00)04013-7.
- Rudd, R., J. Moore-Gillon, and M. Muers. 2002. Mesothelioma, letter to the editor. *Thorax* 57:187. doi:10.1136/thorax.57.2.187.
- Rusch, A., G. Ziltener, K. Nackaerts, W. Weder, S. Ra, and E. Felley-Bosco. 2015. Prevalence of BRCA-1 associated protein 1 germline mutation in sporadic malignant pleural mesothelioma cases. *Lung Cancer* 87:77–79. doi:10.1016/j.lungcan.2014.10.017.
- Seaton, A. 2002. One fibre or many; what causes mesothelioma, letter to the editor. *Thorax* 57:186–87. doi:10.1136/thorax.57.2.186-b.
- Sekido, Y. 2008. Molecular biology of malignant mesothelioma. *Environmental Health and Preventive Medicine* 13:65–70. doi:10.1007/s12199-007-0015-8.
- Selikoff, I. J., and D. H. K. Lee. 1978. *Asbestos and disease*. New York, NY: Academic Press.
- Sneddon, S., J. S. Leon, I. M. Dick, G. Cadby, N. Olsen, F. Brims, R. J. Allcock, E. K. Moses, P. E. Melton, N. De Klerk, A. W. Musk, B. W. Robinson, and J. Creaney. 2015. Absence of germline mutations in BAP1 in sporadic cases of malignant mesothelioma. *Gene* 563:103–05. doi:10.1016/j.gene.2015.03.031.
- Sporn T. A., V. L. Roggli. 2004. Mesothelioma. In *Pathology of asbestos-associated diseases*, 2nd ed., ed. V. I. Roggli, T. D. Oury, and T. A. Sporn, 104–168. New York, NY: Springer.
- Stayner, L. T., D. A. Dankovic, and R. A. Lemen. 1996. Occupational exposure to chrysotile asbestos and cancer risk: A review of the amphibole hypothesis. *American Journal of Public Health* 86:197–186. doi:10.2105/AJPH.86.2.179.
- Steenland, K., C. Burnet, N. Lalich, E. Ward, and J. Hurrell. 2003. Dying for work: The magnitude of US mortality from selected causes of death associated with occupation. *American Journal of Industrial Medicine* 43:461–82. doi:10.1002/(ISSN)1097-0274.
- Szeszenia-Dabrowska, N., U. Wilczynska, W. Szymczak, and A. Strzelecka. 2002. Mortality study of workers compensated for asbestosis in Poland, 1970–1997. *International Journal of Occupational Medicine and Environmental Health* 15:267–78.
- Tannock, I. F. 1983. Biology and tumor growth. *Hospital Practice* 18:91–93. doi:10.1080/21548331.1983.11702514.
- Terracini, B., D. Mirabelli, C. Magnani, D. Ferrante, F. Barone-Adesi, and M. Bertolotti. 2014. A critique to a review on the relationship between asbestos exposure and the risk of mesothelioma. Letter to the editor. *European Journal of Cancer Prevention* 23:492–94. doi:10.1097/CEJ.0000000000000057.
- Testa, J. R., M. Cheung, J. Pei, J. E. Below, Y. Tan, E. Sementino, N. J. Cox, A. U. Dogan, H. I. Pass, S. Trusa, M. Hesdorffer, M. Nasu, A. Powers, Z. Rivera, S. Comertplay, M. Tanji, G. Gaudino, H. Yang, and M. Carbone. 2012. Germline BAP1 mutations predispose to malignant mesothelioma. *Nature Genetics* 43:1022–25. doi:10.1038/ng.912.
- Thomas, A., Y. Chen, T. Yu, A. Gill, and V. Prasad. 2015. Distinctive clinical characteristic of malignant mesothelioma in young patients. *Oncotarget* 6:16766–73. doi:10.18632/oncotarget.4414.
- Tomatis, L., S. Cantoni, F. Carnevale, E. Merler, F. Mollo, P. Ricci, S. Silvestri, P. Vineis, and B. Terracini. 2007. The role of asbestos fiber dimensions in the prevention of mesothelioma. *International Journal of Occupational and Environmental Health* 13:64–69. doi:10.1179/oeh.2007.13.1.64.
- Tossavinen, A. 2004. Global use of asbestos and the incidence of mesothelioma. *International Journal of Occupational and Environmental Health* 10:22–25. doi:10.1179/oeh.2004.10.1.22.
- Toyokuni, S. 2011. Mysterious link between iron overload and CDKN2A/2B. *Journal of Clinical Biochemistry and Nutrition* 10:48–49.
- U.S. Consumer Product Safety Commission. 1977. Ban of consumer patching compounds containing respirable free-form asbestos. 16 CFR Ch. 11 §1304.5 (1-1-04 Ed): 380-383.
- Ugoilini, D., M. Neri, J. Ceppi, A. Cesario, I. Dianzani, R. Filiberti, F. Gemignani, S. Landi, C. Magnani, L. Mutti, R. Puntoni, and S. Bonassi. 2008. Genetic susceptibility to malignant mesothelioma and exposure to asbestos: The influence of the familial factor. *Mutation Research* 658:162–71. doi:10.1016/j.mrrev.2007.08.001.
- Wagner, J. C., C. A. Sleggs, and P. Marchard. 1960. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *British Journal of Industrial Medicine* 17:260–71.
- Wang, X., S. Lin, I. Yu, H. Qiu, Y. Lan, and E. Yano. 2013. Case-specific mortality in a Chinese chrysotile textile worker cohort. *Cancer Science* 104:245–48. doi:10.1111/cas.12060.

- Wolff, H., T. Vehmas, P. Oksa, J. Rantanen, and H. Vainio. 2015. Consensus report: Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: Recommendations. *Scandinavian Journal of Work, Environment & Health* 41:5–15. doi:10.5271/sjweh.3462.
- Wylie, A. G., and P. A. Candela. 2015. Methodologies for determining the sources, characteristics, distribution, and abundance of asbestiform and non-asbestiform amphibole and serpentine in ambient air and water. *Journal of Toxicology and Environmental Health, Part B* 18:1–42. doi:10.1080/10937404.2014.997945.
- Yang, H., J. R. Testa, and M. Carbone. 2008. Mesothelioma epidemiology, carcinogenesis and pathogenesis. *Current Treatment Options in Oncology* 9:147–57. doi:10.1007/s11864-008-0067-z.